DOES ONE NEED TO GRADUALLY INCREASE THE DOSAGE OF ADMINISTERED ESTROGENS IN PATIENTS UNDER LONG-TERM ESTROGEN THERAPY IN ORDER TO MAINTAIN HIGH PROLIFERATION, AND CAN ONE INDUCE A CONSISTENT INTERMEDIATE TYPE OF PROLIFERATION BY ADMINISTERING LOW DOSAGES OF ESTROGENS?

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Since estrogens produce marked vaginal proliferation and progressive differentiation to a completely differentiated superficial layer, one could suppose that by taking the correct dosages of estrogens it should be possible tp produce a consistent intermediate type of proliferation in vaginal smears composed exclusively of intermediate cells.

In 58 castrated or postmenopausal women with complete vaginal atrophy, progressive low dosages of estrogens (estradiol benzoate, diethylstilbestrol, dienestrol, ethynylestradiol) were administered and tested by repeated vaginal smears. The results showed that when the dosage reached the minimal effective level, the vaginal epithelium started to grow. The prior atrophic smear changed progressively to a subatrophic smear (mixture of atrophic or basal and intermediate cells), and then with increase of the dosage, the intermediate cells became the predominant cell elements of the smear. If the estrogens were then continued with the same dosage which had induced the intermediate smear type, one would expect to obtain a persistence of this intermediate smear type. Unfortunately, the control tests did not support this hypothesis. Indeed, the smear continued to change and there appeared superficial cells with pyknosis and even some eosinophilic superficial cells. Even if the estrogens were stopped immediately after the first appearance of the intermediate type, the smear generally continued to show a progressive differentiation to a more superficial type for a few days. After this, it returned progressively to an intermediate type, which persisted for a few days up to several weeks, then to the subatrophic and, finally, to the completely atrophic type of the beginning.

If the estrogens were administered with increasing dosages up to the point where they produce subatrophic smears, and if the increase was then discontinued and the estrogens administered only with the same dosage for several days or weeks, only transitory smear pictures of the intermediate type could be observed.

If the estrogens were administered up to a dosage producing the first intermediate type, then stopped, it was not possible to obtain in every case a consistent intermediate type of proliferation either by giving estrogens with the same dosage or even with a lower dosage from time to time for several days. One observes a continuous up and down of the smears from the intermediate to a more superficial or to a subatrophic type.

Only in 7 cases was a continuous intermediate type of smear observed, with continuous dosage of estrogens above the first minimal "intermediate" dosage; but in these cases cytolysis had appeared, destroying the outer cell layers and thus prohibiting the differentiation to superficial cells.

From these experiences it can be concluded that under normal conditions, especially if cytolysis does not occur, it is very difficult to obtain, with low dosages of estrogens, a consistent intermediate vaginal smear type in the castrated or postmenopausal woman. It seems that the proliferation and especially the differentiation of the vaginal epithelium induced by estrogens has immediately a more complete tendency or that the minimal dosages required to produce karyopyknosis or only intermediate cells are nearly the same. In other words, it seems that if the estrogens are just sufficient to produce an intermediate layer or the first degree of vaginal differentiation, such a vaginal epithelium has immediately the tendency to arrive at a more complete differentiation, as shown by the progressive retraction of the nucleus and the rapid formation of superficial cells, even if the typical intermediate cell layers at biopsy have reached only a moderate thickness. This tendency distinguishes the vaginal effect of estrogens from that of other hormones like testosterone and progesterone, which are able to induce only the first degree of differentiation, or an intermediate layer; and an increase of the dosage does not produce the second degree of differentiation or karyopyknosis and eosinophilia, but only an increase of the thickness of the intermediate layer.

For these reasons, I believe that the continuous spontaneous smears of purely intermediate type which can be observed without cytolysis in cases of amenorrhea or after castration or menopause do not have an exclusive estrogenic origin, but that other hormones interfere, especially androgens, which increase the proliferation and glycogenization induced by estrogens by a synergistic mechanism, but block the differentiation to superficial cells by the specific anti-estrogenic antagonism.

During long-term administration of estrogens, either for castration symptoms or for treatment of endometriosis or cancer metastases, etc., the vaginal smear can present different reactions:

1. With moderate dosages of estrogens, the vaginal epithelium presents rapidly an important estrogen effect with pyknosis up to 90% and eosinophilia to 70% or more. The continuation of these dosages (examples: 10 mg. of estradiol enanthate I. M. every two weeks; 10 mg. of diethylstilbestrol fureate I. M. every two weeks; 2-4 mg. per day per os of diethylstilbestrol or dienestrol) even for months produces identical vaginal reactions. It is not necessary to progressively increase the dosage in order to obtain an identical vaginal reaction. In some cases, especially if the dosage is relatively low (just sufficient to produce an Eosinophilic and Pyknotic Index of about 50% at the beginning) one can observe after a while an increase of these indices, which can be explained by a storage phenomenon of the estrogens in the body. The typical example is presented by castrated patients treated by the implant of a 100 mg. pellet of diethylstilbestrol, for which the daily resorption rate varies between 0.5 and 0.9 mg. 21 patients received such an implant every 8-12 months for over 5 years and the vaginal cytology showed identical reactions after each pellet, as demonstrated in previous papers (1, 2, 3).

In some patients after the menopause or after castration a progressive diminution of the vaginal estrogenic reactions was observed after daily administration of 2 mg. of dienestrol per os. But the vaginal smear then showed a particular cytological picture and control tests of the urinary 17-ketosteroids showed that this decrease of the pyknosis and eosinophilia was possible due to a stimulation of the adrenal production of androgens by the estrogen treatment. The apparent diminution of the estrogen effect in the vaginal smear seems, therefore, not to be related to a lowering of the vaginal sensitivity to estrogens, but caused by the antagonistic effect of the androgens against estrogens.

2. The findings are different if the patients receive high dosages of estrogens, as for example over 15-25 mg. of diethylstilbestrol or dienestrol per os per day over several weeks. In these cases, the vaginal smear at the beginning shows a normal response to estrogens, with a rise of the Pyknotic and Eosinophilic Indices to nearly 100%. But, if the treatment is continued over 1-2 weeks, the vaginal smear shows a progressive decrease of the pyknosis and eosinophilia. For a while this decrease can be stopped by an increase of the estrogen dosage, but finally a further increase of the estrogen dosage has no effect upon the vaginal smear, which tends to a regressive and nearly subatrophic type. The same regressive phenomenon can be observed after massive treatment with androgens or progesterone, and seems to be related to a progressive exhaustion of the vaginal proliferative and maturation potential under extremely high hormonal stimulation.

Conclusions: Under long-term estrogenic treatment, the vagina continues to react normally to administered estrogens as long as the dosage remains within physiological limits. Abnormally high dosages continued over several weeks are followed by a decrease of the vaginal receptivity to estrogens.

Bibliography

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DISCUSSION

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Pundel has written a very excellent summary to these two questions and I am in complete agreement. It is very difficult to obtain a consistent intermediate vaginal cell pattern with continuous administration of low dosages of estrogens. Since the effect of estrogen on the vaginal mucosa is both proliferation and differentiation, it is an unusual experience to be able to separate these effects. Rarely, in an exceptional patient and particularly using the weaker estrogens, one can obtain an intermediate effect for a limited period of time. Much more common is the "continuous up and down" that Pundel describes.

The various types of reactions to long-term estrogen therapy are accurately described. While these are the fundamental and basic patterns, they will vary in different patients with different endocrine and disease status and with different type, dosage, and route of administration of the hormone (viz., local vs. systemic administration).

CLOSING REMARKS

J. PAUL PUNDEL, Luxembourg, Luxembourg:

No comments.

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